2 SYNOPSIS

Sponsor: **Reckitt Benckiser Pharmaceuticals Inc.**	**Individual Study Table Referring to Part of the Dossier**	~~**(For National Authority Use only)**~~
Name of Finished Product: RBP-6300	**Volume:**	
Name of Active Ingredient: **RBP-6300 (buprenorphine hemiadipate HCl and naloxone HCl dihydrate in a 1:1 ratio)**	**Page:**	

Study Title:
A Randomised, Double-Blind, Double-Dummy, Active-Drug-Controlled, Parallel-Group, Multicentre Acceptability and Safety Study of the Transfer from Subutex®/Suboxone® to RBP-6300 in Opioid-Dependent Subjects

Investigators and Study Centres: 16 centres (see Appendix 16.1.4). Two sites in Austria underwent study initiation, but did not receive study medication and were not active study sites.

Publication (reference): None

Studied Period:

12 March 2012 (first subject enrolled) to
29 November 2012 (last subject completed)

Phase of Development: Phase 2

Objectives:

Primary: To demonstrate that RBP-6300 was not inferior to Subutex®/Suboxone® as assessed by the peak change from baseline in the pre-dose Clinical Opiate Withdrawal Scale (COWS) score during the Double-Blind Transfer Phase.

Secondary: The secondary objectives of this study were to assess the overall clinical response to RBP-6300 with respect to the following:

- Mean change from baseline (Day 1) in the pre-dose COWS score during the Double-Blind Transfer Phase
- Mean change from baseline (Day 1) in the COWS score during the first 2 hours post-dosing on Day 1 of the Double-Blind Transfer Phase
- Mean change from baseline (Day 8) in the pre-dose COWS score during the Single-Blind Transition Phase
- Mean change from baseline (Day 8) in the COWS score during the first 2 hours post-dosing on Day 8 (Day 1 of the Single-Blind Transition Phase)

- Peak and mean change from baseline in the pre-dose Subjective Opiate Withdrawal Scale (SOWS) scores
- Illicit opioid and non-opioid drug use as measured by urine drug screen (UDS)
- Drug craving as assessed using a 100 mm visual analogue scale (VAS)
- Illicit opioid and non-opioid drug use as measured by self-reporting on the Substance Use Inventory (SUI)
- Incidence of withdrawal due to clinically significant difficulties (subject required rescue medication or dose escalation)
- Treatment compliance rate (compliance with the treatment regimen in the protocol)
- Treatment retention rate (attendance at the study site according to the study schedule)

Further secondary objectives were as follows:

- To evaluate the safety and tolerability of RBP-6300 in terms of adverse events (AEs), clinical laboratory tests, vital signs, concomitant medication use, and change from baseline in the Columbia-Suicide Severity Rating Scale (C-SSRS)
- To assess the steady-state pharmacokinetics of buprenorphine, norbuprenoprhine, naloxone and naloxone-3-glucoronide following the administration of 7 days of once-daily dosing with oral RBP-6300

Methodology: This was a randomised, double-blind, double-dummy, 2-arm, active drug-controlled, parallel-group, multicentre study of the acceptability and safety of transfer from Subutex/Suboxone (buprenorphine HCl) to RBP-6300 (buprenorphine hemiadipate HCl) in opioid-dependent subjects previously receiving a stable dose of Suboxone or Subutex. The study included a 7-day open-label Subutex/Suboxone run-in phase (Open-Label Run-in Phase), a 7-day, active, drug-controlled, double-blind and double-dummy transfer phase (Double-Blind Transfer Phase), and a 3-day single-blind Subutex/Suboxone transition phase (Single-Blind Transition Phase), with a final assessment visit on the day after the last dose of study drug was administered and a follow-up visit 5 to 10 days later.

Open-Label Run-in Phase (Days -7 to -1): At the screening visit (Day -7), written informed consent was obtained and inclusion/exclusion criteria reviewed. Assessments included demographics, medical history, prior/concomitant medications; a complete physical examination with height and weight; vital signs (sitting blood pressure, pulse, and respiratory rate); 12-lead electrocardiogram (ECG); virology tests for human immunodeficiency virus (HIV) and hepatitis B and C; routine laboratory tests (blood chemistry, haematology, and urinalysis); a urine pregnancy test (β-human chorionic gonadotropin [β-hCG]) for women of childbearing potential (serum pregnancy test if required as per local regulations); UDS; COWS, SOWS, drug-craving VAS, SUI for the preceding 30 days, and C-SSRS. Adverse events were recorded at each study visit. Following these procedures, each subject received sublingual Subutex or Suboxone at 8 mg/day, 16 mg/day, or 24 mg/day, depending on the dose level for that subject on entry to the study. The initial dose of open-label study drug was administered under observation.

On Day -4, the drug accountability diary and compliance with study treatment were checked, prior/concomitant medications were reviewed; vital signs (sitting) recorded, UDS obtained, and COWS, SOWS, drug-craving VAS, and SUI administered.

Double-Blind Transfer Phase (Days 1-7): In this phase, subjects were transferred without a washout period to double-blind treatment with either sublingual Subutex/Suboxone at the dose they were taking during the Open-Label Run-in Phase plus RBP-6300 placebo or oral RBP-6300 at the corresponding dose equivalent of buprenorphine plus Subutex/Suboxone placebo. Subjects were randomly assigned to 1 of the treatment groups in a 1:1 ratio. Randomisation was stratified by site and by prior Subutex/Suboxone dose to try to ensure that a minimum of approximately 20% of subjects were randomised at each dose level. Pre-dose procedures performed on Day 1 included review of inclusion/exclusion criteria, drug accountability diary, and prior/concomitant medications; medical history updates; a partial physical examination with weight; vital signs (sitting); urine β-hCG for females of childbearing potential; UDS; administration of COWS, SOWS drug-craving VAS, SUI, and C-SSRS; and pharmacokinetic (PK) blood sampling. Measurements of COWS, SOWS, and drug-craving VAS scores were also obtained at 1 and 2 hours (± 15 minutes) post-dose. Study treatment was administered under observation each day of the double-blind phase. Adverse events were recorded at each study visit.

On Days 2-7, pre-dose assessments included review of study treatment compliance/drug accountability and prior/concomitant medications; vital signs (sitting); UDS; COWS, SOWS, drug-craving VAS, and SUI; and PK blood sampling.

Single-Blind Transition Phase (Days 8-10): Subjects were returned to treatment with Subutex/Suboxone administered on a single blind basis at the same dose taken during the Open-Label Run-in Phase. The last dose of study medication was administered on Day 10. The pre-dose procedures performed during this phase were review of medication compliance/drug accountability and prior/concomitant medications; vital signs (sitting); UDS; and COWS, SOWS, and SUI. On Day 8, a pre-dose blood sample was obtained for PK measurements, the C-SSRS was administered pre-dose, and a 12-lead ECG and partial physical examination (with weight) were also performed. Assessments of COWS, SOWS, and drug-craving VAS were also obtained at 1 and 2 hours (± 15 minutes) post-dose. Adverse events were recorded at each study visit.

Final Assessment Visit (Day 11): Following the final dose of study medication, prior/concomitant medications were reviewed, vital signs (sitting) taken, a partial physical examination (with weight) performed, a UDS and clinical laboratory tests including a β-hCG test for women of childbearing potential obtained , and AEs recorded. Assessments of COWS, SOWS and drug-craving VAS scores, SUI, and C-SSRS were also obtained. Subjects resumed the treatment they had received prior to study entry or started another treatment under the care of their personal physicians.

Follow-up Visit: Follow-up assessments were completed between Day 15 and Day 20. These included a review of prior/concomitant medications, a 12-lead ECG, AEs, C-SSRS, a follow-up questionnaire, and treatment status.

Number of Subjects (Planned and Analysed):
Approximately 140 subjects were planned (70 subjects per group); 143 subjects were randomised of which 142 were analysed for safety; 142 subjects were analysed for efficacy.

Diagnosis and Main Criteria for Inclusion:
Potential subjects (male or non-pregnant, non-lactating females ≥18 years of age) were required to meet the Diagnostic and Statistical Manual of Mental Disorders, 4th ed., Text Revision (DSM-IV-TR) criteria for opioid dependence, must have been receiving maintenance treatment with Suboxone/Subutex at stable doses of 8, 16, or 24 mg/day for ≥30 days prior to screening, and be considered by the investigator to be suitable for continuing such treatment. Female subjects of childbearing potential had to have a negative urine β-hCG or plasma (dependent on local regulations) test prior to enrollment.

Test Product, Dose and Mode of Administration, Lot Number:
RBP-6300 (buprenorphine hemiadipate) was provided by the sponsor as 10-mg tablets to be swallowed whole with water during the Double-Blind Transfer Phase according to dose level: 10 mg/day (Dose Level 1), 20 mg/day (Dose Level 2), or 30 mg/day (Dose Level 3). Lot numbers were as follows:

[redacted]

Suboxone and Subutex (buprenorphine HCl) were provided by the sponsor as 8-mg tablets to be taken sublingually according to dose level: 8, 16, or 24 mg/day. Lot numbers were as follows:

Open-label Subutex: [redacted]

Blinded Subutex: [redacted]

Open-label Suboxone: [redacted]

Blinded Suboxone [redacted]

The active ingredients in RBP-6300 were buprenorphine hemiadipate HCl and naloxone HCl dihydrate. Naloxone HCl dehydrate was added in amounts equivalent to buprenorphine hemiadipate HCl to reduce the potential for parenteral abuse. Both Suboxone and Subutex comprised 8 mg buprenorphine HCl as the active ingredient. Suboxone also contained 2 mg of naloxone HCl dehydrate.

Duration of Treatment: 17 days: 7-day Run-In Phase, 7-day Double-Blind Transfer Phase, and 3-day Single-Blind Transition Phase

Reference Therapy, Dose and Mode of Administration, Lot Number:
Oral RBP-6300 placebo tablets were identical in content and appearance to RBP-6300 10-mg tablets except that they lacked the active ingredients. Lot numbers were as follows:

[redacted]

Sublingual Subutex placebo tablets were identical in content and appearance to 8-mg Subutex tablets except that they lacked the active ingredient. Lot numbers were as follows:

[redacted]

Sublingual Suboxone placebo 8-mg tablets were identical in content and appearance to 8-mg Suboxone tablets except that they lacked the active ingredients. Lot numbers were as follows:

[redacted]

All placebo tablets were provided by the sponsor.

Criteria for Evaluation:

Efficacy:
Efficacy assessments were as follows:

- COWS
- SOWS
- Drug-craving VAS
- UDS
- SUI

Safety:
Safety assessments were as follows:

- AE monitoring
- Routine clinical laboratory tests (serum chemistry, haematology, and urinalysis)
- Vital signs after sitting for at least 5 minutes (blood pressure, pulse, respiratory rate)
- Physical examinations, including weight
- Prior/concomitant medication monitoring
- C-SSRS

Pharmacokinetics:

Plasma PK levels were determined in all randomised subjects who received study drug and from whom at least 1 blood sample was taken for PK determination. The PK blood samples were taken at pre-dose on each day of the Double-Blind Transfer Phase and on the first day of the Single-blind Transition Phase. The PK trough concentrations for buprenorphine, norbuprenorphine, naloxone, and naloxone-3-glucuronide from the 7-day Double-Blind Transfer Phase were presented. An ad-hoc analysis was performed using the trough PK samples for buprenorphine and naloxone to evaluate steady state attainment and dose-proportionality.

Statistical Methods:
All tables, statistical analyses, figures, and subject data listings were generated using SAS® Version 9.1.3 or later (SAS Institute Inc., Cary, North Carolina, United States of America).

With the exception of the non-inferiority evaluation (which was done by using a one-sided significance level of 0.025), all statistical tests were 2-sided at a significance level of 0.05. Adjustments were not made for performing multiple comparisons. No formal hypothesis

testing was performed on the demographic and baseline characteristics data; however, formal statistical comparisons between treatment groups were performed on the efficacy data and selected safety data.

For the purposes of the analyses of data collected during the Double-Blind Transfer Phase, all values obtained prior to the administration of the first dose of double-blind study medication were eligible to be used as the baseline value. For analyses of data collected during the Single-Blind Transition Phase, data collected during the Double-Blind Transfer Phase which were closest, but prior to the time of the administration of the first dose of single-blind study treatment, were used as the baseline values.

Non-inferiority was claimed if the upper bound of the 95% confidence interval (CI) for the difference in the mean peak increase from baseline in COWS score lay entirely below the non-inferiority margin of +6 points. The sample size was based on the primary efficacy endpoint, which was the peak increase from baseline in the pre-dose COWS score over the 7-day Double-Blind Transfer Phase (Days 2 to 8). Assuming an SD for the peak change from baseline of 6.0 and the mean peak change from baseline in the RBP-6300 +Subutex/Suboxone placebo group to be no more than 3 points on the COWS scale greater than that in the RBP-6300 placebo + Subutex/Suboxone group, 63 subjects per treatment group provided 80% power to demonstrate non-inferiority at a significance level of 0.05. Based on an estimate of up to a 10% dropout rate, a total of 140 eligible subjects (70 subjects in each of the 2 treatment groups) were required.

The following analysis populations were defined for this study:

The Intent-to-Treat (ITT) population consisted of all randomised subjects who received at least one dose of study treatment during the Double-Blind Transfer Phase and had at least one post-baseline pre-dose COWS score available on Days 2-8.

The Per-Protocol (PP) population consisted of all subjects in the ITT population who did not have any major protocol violations.

The Safety population consisted of all randomised subjects who received at least 1 dose of study treatment during the Double-Blind Transfer Phase. Subjects were included in the safety analyses according to the actual treatment they received.

The PK population included all randomised subjects who received study drug and from whom at least 1 blood sample for PK determination was taken.

Efficacy:

The primary efficacy endpoint was the peak increase from baseline in the COWS score over the 7-day Double-Blind Transfer Phase (Days 2-8). The peak increase was analysed by an analysis of covariance (ANCOVA) model which included a term for randomised treatment and baseline COWS score as the covariate. The difference between treatments in mean peak increase in COWS score [(RBP-6300 +Subutex/Suboxone placebo) - (RBP-6300 placebo + Subutex/Suboxone)] and the associated 95% CI were presented. The primary efficacy

analysis was performed on both the ITT and PP populations.

An exploratory analysis of the primary endpoint was also performed using a different ANCOVA model which included terms for randomised treatment, study site, stabilisation treatment at entry to the study, Subutex/Suboxone dose level received during the Open-Label Run-in Phase, interaction terms for treatment by study site, treatment by stabilisation treatment, treatment by Subutex/Suboxone dose level, stabilisation treatment by dose level, and baseline COWS score as a covariate.

The secondary efficacy endpoints were summarised and analysed for both the ITT and PP populations. Mean change from baseline in COWS score during the Double-Blind Transfer Phase and the Single-Blind Transition Phase was analysed by an ANCOVA model with randomised treatment as the fixed effect and baseline value as the covariate.

Other secondary variables included the peak increase and mean change from baseline in SOWS scores as defined for both the primary efficacy variable and the mean change from baseline in COWS scores; the number and percentage of subjects with an opioid-free UDS, with the differences between groups analysed by Fisher's exact test; drug-craving VAS at time points defined for the mean change from baseline in COWS scores; SUI results summarised for each phase, with the differences between groups analysed by Fisher's exact test; the incidence of withdrawal due to clinically significant difficulties (e.g., subjects requiring rescue medication or dose escalation); the number and percentage of subjects who took their assigned study treatment; and the number and percentage of subjects who visited the study site according to the schedule in the protocol. The compliance rate was summarised by using the number and percentage of subjects who took their assigned study treatment according to the protocol, and the difference between groups was analysed using Fisher's exact test.

Results of additional exploratory analyses on the peak increase from baseline in the pre-dose COWS score, and peak increase from baseline in the pre-dose SOWS score, are provided in an addendum to the CSR.

Safety:
Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary, Version 15.0.

Because all subjects were on a stable dose of Suboxone or Subutex for at least 30 days prior to the run-in phase and remained on buprenorphine alone or in combination with naloxone throughout the study, AEs reported following initiation of randomised study treatment were considered treatment-emergent AEs (TEAE). Treatment-emergent AEs also included AEs that were present prior to randomised study treatment but increased in frequency or severity following initiation of treatment. Adverse events with partial or missing start dates were considered TEAEs unless the non-missing components confirmed otherwise.

Treatment-emergent AEs were summarised by treatment group, system organ class (SOC) and preferred term (PT). An overall summary of the number and percentage of subjects with

at least 1 TEAE, related TEAE, SAE, related SAE, TEAEs leading to discontinuation of study treatment, and deaths were presented by treatment group. In addition, summaries of the number and percentage of subjects with TEAEs were presented by SOC and PT for all TEAEs, related TEAEs, serious TEAEs, serious related TEAEs, TEAEs leading to discontinuation of study treatment, and TEAEs leading to death. Treatment-emergent AEs were also summarised by treatment group, SOC, PT, and maximum severity.

Clinical laboratory data (haematology, serum chemistry, and urinalysis) were summarised by treatment group for each visit using descriptive statistics. Summaries of the change from baseline and shift tables displaying shifts below, within, and above normal ranges were produced. Vital signs were summarised by randomised treatment for each scheduled visit.

The results obtained from the 12-lead ECG were classified as normal, abnormal not clinically significant, abnormal clinically significant, or not done. The number and percent of subjects having results within each of these categories were presented by treatment group for each scheduled visit.

Physical examination and follow-up questionnaire data were provided as by-subject listings only. Prior and concomitant medications were coded using the 01 MAR2012 version of the World Health Organization Drug Dictionary (WHO Drug) and summarised by anatomical therapeutic chemical (ATC) classification categories by treatment group.

Results from the C-SSRS were collected at screening and summarised by treatment group, with descriptive statistics presented for numbers of attempts, aborted attempts, and interrupted attempts. The number and percentage of subjects with any form of suicidal ideation or behaviour were presented for each time point by treatment group.

Pharmacokinetics:

The mean and SD of the plasma trough concentrations (C_{trough}) of buprenorphine, norpubrenorphine, naloxone, and naloxone-3-glucuronide during the 7-day Double-Blind Transfer Phase were plotted using linear scales, presented and summarized in tables and listings.

Attainment of steady-state was evaluated for buprenorphine and naloxone using a repeated-measures analysis (Helmert's contrasts) method during 7-day Double-Blind Transfer Phase. Once steady state was reached the power model was used to investigate the dose proportionality of for buprenorphine and naloxone.

Summary of Results

Efficacy:

- RBP-6300 was non-inferior to Subutex/Suboxone in the treatment of opioid-dependent subjects based on a comparison of peak increase from baseline in COWS score. The estimated LSM difference (RBP-6300-Subutex/Suboxone) between treatment groups in peak increase from baseline in COWS score was 1.45 with 95% CI: (0.54, 2.36) for the PP population, and 1.26 with 95% CI: (0.43, 2.08) for the ITT population. The upper

95% CI limit was well below the non-inferiority margin of 6 for both the PP and ITT populations, thus demonstrating the non-inferiority of RBP-6300 to Subutex/Suboxone.

The above finding was generalisable to subjects who had been stabilised on either Subutex or Suboxone at different dose levels prior to switching to RBP-6300.

- Subjects in both the RBP-6300 and Subutex/Suboxone treatment groups had comparable scores for COWS, SOWS, and drug-craving VAS at pre-dose and appeared well-stabilised on their current treatment.
- Subjects in the RBP-6300 group returned to their pre-dose treatment in the Single-Blind Transfer Phase without any apparent destabilizing effect, confirming that RBP-6300 was well-matched to Subutex/Suboxone in the treatment of opioid-dependent subjects.
- There were no statistically significant differences between RBP-6300 and Subutex/Suboxone in changes from baseline pre-dose to either 1- or 2-hours post-dose assessments of COWS, SOWS and drug-craving VAS, at the beginning and at the end of the Double-Blind Transfer Phase.
- RBP-6300 and Subutex/Suboxone treatment groups showed similar changes from baseline pre-dose to daily pre-dose assessments of COWS, SOWS and drug-craving VAS during the Double-Blind Transfer Phase and the Single-Blind Transition Phase.
- There were no statistically significant differences between RBP-6300 and Subutex/Suboxone in changes from baseline pre-dose to the final assessment in clinical and subjective assessments of opioid withdrawal symptoms and assessment of drug-craving.

Pharmacokinetics:

- Results and conclusions for the PK analyses will be included in an addendum to this clinical study report.

Safety:

- A total of 42 (56.0%) subjects in the RBP-6300 group and 33 (49.3%) in the Subutex/Suboxone group experienced a TEAE. The difference between treatment groups was not statistically significant (p=0.422).
- In the RBP-6300 group the most common TEAEs were diarrhoea (n=7), drug withdrawal syndrome (n=7), hyperhidrosis and upper abdominal pain (n=5 each). In the Subutex/Suboxone group the most common TEAEs were nasopharyngitis (n=7), headache (n=7), and nausea (n=4).
- The majority of subjects in both groups reported TEAEs that were of mild or moderate intensity. Five subjects in total experienced a severe TEAE, 3 in the RBP-6300 group and 2 in the Subutex/Suboxone group.
- Nine (12.0%) subjects in the RBP-6300 group and 6 (9.0%) in the Subutex/Suboxone group experienced TEAEs judged by the investigator to be related to study drug.

- Two subjects in the RBP-6300 group experienced an SAE each. Both events (abortion spontaneous, severe acute psychosis) occurred after discontinuation of study drug and both were judged not related to study drug by the investigator. No SAEs were reported in the Subutex/Suboxone group.
- Six subjects discontinued study drug due to a TEAE. Five (6.7 %) subjects in the RBP-6300 group discontinued due to chills, myalgia, dyspnea and hyperhidrosis (n=1), psychiatric decompensation (n=1), acute psychosis (n=1), fatigue (n=1), and drug withdrawal syndrome (n=1). All of these events except fatigue were judged not related to study drug. One subject discontinued in the Subutex/Suboxone group due to an AE of drug withdrawal syndrome which was judged not related to study drug.
- No deaths occurred during the study.
- No notable changes in vital signs or haematology, serum chemistry and urinalysis values, and no clinically significant abnormalities in ECG parameters were observed in either treatment group.
- No occurrence of suicidal ideation or suicidal behaviours of any type were reported during the treatment period.

CONCLUSIONS

Efficacy Conclusions:

Oral treatment of opioid withdrawal symptoms and drug-craving with RBP-6300 (buprenorphine/naloxone) was found to be non-inferior to sublingual treatment with Subutex (buprenorphine) or Suboxone (buprenorphine/naloxone) in opioid-dependent subjects.

The above finding was generalisable to subjects who had been stabilised on either Subutex or Suboxone at different dose levels prior to switching to RBP-6300.

Pharmacokinetic Conclusions:

Results and conclusions for the PK analyses will be included in an addendum to this clinical study report.

Safety Conclusions:

The safety profile of RBP-6300 was similar to that of Subutex/Suboxone. The type and incidence of TEAEs observed in both groups was expected for this subject population on buprenorphine/naloxone treatment. The incidence of gastrointestinal disorders was slightly higher in the RBP-6300 group (n=12; 16.0%) than in the Subutex/Suboxone group (n=8; 11.9%) which may be expected with an oral drug compared with a sublingual drug. The treatment groups did not differ appreciably in AEs experienced in any of the other SOCs or in AE severity and relatedness to study drug, SAEs, changes in vital signs, laboratory findings, or ECG abnormalities.

Final Report Date: 27 June 2013